Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors.

Bibliographic Source(s)

Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, Strecker MN, Roberts JS, Burke W, Mayeux R, Bird T, American College of Medical Genetics and the National Society of Genetic Counselors. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011 Jun;13(6):597-605. [118 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Guidelines

- Pediatric testing for Alzheimer disease (AD) should not occur. Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation.
- Genetic testing for AD should only occur in the context of genetic counseling (in-person or through video conference) and support by someone with expertise in this area.
  Symptomatic patients: Genetic counseling for symptomatic patients should be performed in the presence of the individual's legal guardian or family member.

  Asymptomatic patients: A protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's chorea Guidelines is recommended.
- Direct to consumer (DTC) *APOE* testing is not advised.
- A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death. Medical records should be used to confirm AD diagnosis when feasible. The history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.
- A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with early onset AD

(EOAD) or late onset AD (LOAD) and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.

- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
  - The lifetime risk of AD in the general population is approximately 10%–12% in a 75- to 80-year lifespan.
  - The effect(s) of ethnicity on risk is still unclear.
  - Although some genes are known, there are very likely others (susceptibility, deterministic, and protective) whose presence and effects are currently unknown.

For Families in which an Autosomal Dominant AD Gene Mutation is a Possibility

- Discuss the risk of inheriting a mutation from a parent affected with autosomal dominant AD is 50%. In the absence of identifying a mutation in apparent autosomal dominant families, risk to offspring could be as high as 50% but may be less.
- Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations:
  - A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption)
  - Autosomal dominant family history of dementia with one or more cases of EOAD
  - A relative with a mutation consistent with EOAD (currently *PSEN1/2* or *APP*)

  The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted (see www.molgen.ua.ac.be/ADMutations/) before disclosure of genetic test results, and specific genotypes should not be used to predict the phenotype in diagnostic or predictive testing. See Table 2 in the original guideline document for a list of additional AD web-based resources.

- Discuss the likelihood of identifying a mutation in *PSEN1*, *PSEN2*, or *APP*, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.
- Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing tested, the option of deoxyribonucleic acid (DNA) banking should be discussed.

For Families in which Autosomal Dominant AD is Unlikely

- Inform them why their family history is consistent with familial or sporadic AD.
- Discuss that both sporadic and familial cases can be due to a genetic susceptibility. Risk estimates are only available for first-degree relatives of an affected individual in sporadic or familial cases.
- Genetic testing for susceptibility loci (e.g., *APOE*) is not clinically recommended due to limited clinical utility and poor predictive value. If a patient wishes to pursue testing despite genetic counseling and recommendations to the contrary, testing may be considered at the clinician's discretion. Testing performed should follow the Huntington disease (HD) genetic testing guidelines, with emphasis on genetic counseling with a qualified clinician. As such, DTC genetic testing is not advised.
- Motives and considerations for pursuing genetic testing should be explored. This counseling should be an exploration of personal experiences, value and beliefs, and personal and family needs. Genetic testing should be discussed within the context of adapting to familial risk and when clients feel compelled to learn a more refined estimate of their risks to enhance their quality of life. As part of this, it is helpful to lead the individual through the scenario of receiving a positive test result and a negative test result, having them assess the ways these results would positively or adversely impact their psyche, life plans, and relationships.
  - Symptomatic patients: Because genetic testing of a symptomatic individual is typically requested by a relative concerned about his risk, the counselor must remain alert to any potential conflicts of interest, such as lack of interest of the symptomatic patient or of other at-risk family members. If the symptomatic patient gives any inclination of being averse to testing, it is not recommended. Instead, DNA banking should be explored.

    If there is disagreement within the family regarding whether testing should be performed, a family meeting is strongly encouraged (with or without the genetic counselor present). A family meeting would allow all interested parties to discuss the potential impact of the genetic testing on the family, how test results will be communicated, and how to respect the rights of those family members who do not wish to know the results.

- Genetic testing: In the event testing is chosen, the following is recommended:
  - Asymptomatic patients should receive a neurologic examination to assess for signs of dementia and to establish a baseline.
  - Assess patient's and any accompanying family member's psychological state of mind. In the case of presymptomatic testing, a consultation with a psychologist/psychiatrist may be recommended for the patient as part of the HD testing approach.

        - If the patient seems to suffer from, or is potentially at risk for, significant psychological/psychiatric problems, consider a psychotherapy referral before testing.
        - If the psychological assessment suggests testing is not in the person's current best interest (e.g., untreated depression or recent death), these reservations should be shared openly, and an agreement should be made to revisit testing once the underlying condition and/or stressors have diminished. A referral for psychotherapy may also be appropriate.
    - Assess and review the psychosocial impact of testing on the patient and his/her family.
        - Reinforce results cannot be "taken back" (although an individual can decide not to learn his or her test results after having the test performed.)
    - Discuss testing logistics, associated costs, and possible outcomes.
        - For EOAD genes, determine best approach to testing for patient (i.e., stepwise testing beginning with *PSEN1* as the most likely gene or ordering a panel).
        - Discuss where results will be kept (e.g., medical record).
        - Determine who will accompany the patient to the result session for support.
        - Discuss possible test outcomes (positive, negative, or variant of uncertain significance). If testing for *APOE*, consider whether you will report other disease risk implications. If so, these should be included in the discussion of test outcomes with the patient. Also, it should be reiterated that *APOE* is a susceptibility gene and is not a predictive test. Thus, individuals with no copies of the ε4 allele still face a 2- to 4-fold increased lifetime risk of developing AD if they have a first-degree relative with AD.
    - Assist the patient and participating family members with informed decision making regarding whom, if anyone, they plan to share the results with and how. Inform about the importance of discretion when discussing genetic testing and results.
    - Discuss the potential impact of genetic test results on insurance, and the benefits and limitations of existing state and federal genetic discrimination legislation.
    - Obtain informed consent for all genetic testing for AD.
    - After results disclosure, revisit the individual's plans regarding with whom and how the results will be shared.
    - Arrange for a follow-up plan to "check in" with the patient and, if relevant, participating family member, and determine whether another genetic counseling session would be beneficial to the patient and/or the patient's partner/family members/friends.
- Discuss the availability and status of AD research and/or DNA banking.

Clinical Algorithm(s)

Protocols for genetic testing (symptomatic testing and predictive testing) for Alzheimer disease are provided in the original guideline document.

Scope

Disease/Condition(s)

Alzheimer disease

Guideline Category

Counseling

Evaluation

Risk Assessment

Screening

Clinical Specialty

Family Practice

Geriatrics

Internal Medicine

Medical Genetics

Neurology

Psychiatry

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

Guideline Objective(s)

To provide clinicians with a framework for assessing their patients' genetic risk for Alzheimer disease (AD), identifying which individuals may benefit from genetic testing, and providing the key elements of genetic counseling for AD, which is an integral part of the testing protocol

Target Population

Individuals who may benefit from genetic counseling and testing for Alzheimer disease

Interventions and Practices Considered

1. Family history
2. Risk assessment by pedigree analysis
3. Obtaining informed consent for genetic testing
4. Pediatric testing for Alzheimer disease (AD) (not recommended)
5. Neurological examination
6. Psychological assessment and referral
7. Genetic testing for AD in adults, in the context of genetic counseling
    - Testing for susceptibility loci (*APOE*) (not recommended)
    - Direct-to-consumer genetic testing (not recommended)
    - Genetic testing for *PSEN1*, *PSEN2*, *APP*, known familial mutations
8. Deoxyribonucleic acid (DNA) banking
9. Post-test results counseling and follow-up

Major Outcomes Considered

- Risk of developing Alzheimer disease (AD)

- Risks and benefits of genetic testing for AD

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline authors searched PubMed for the time period of 1990 to December 31, 2010. The search terms used were: Alzheimer's disease genetics, hereditary Alzheimer's disease, Alzheimer's disease. There were no exclusions.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The practice guidelines of the National Society of Genetic Counselors (NSGC) and the American College of Medical Genetics (ACMG) are developed by members of the NSGC and ACMG to assist geneticists, genetic counselors, and other health care providers in making decisions about appropriate management of genetic concerns, including access to and/or delivery of services. Each practice guideline focuses on a clinical or practice-based issue, and is the result of a review and analysis of current professional literature believed to be reliable.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is not specifically stated for each recommendation.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate counseling of patients on hereditary risk and genetic testing for Alzheimer disease

Potential Harms

- Issues of potential genetic discrimination in light of limitations to current state and federal genetic discrimination legislation for individuals with positive test results
- With respect to asymptomatic individuals, there are concerns genetic testing may trigger an untoward psychological response, such as severe depression, anxiety, or even suicidal ideation. However, research studies and clinical experience indicate that the majority of those tested using a standardized counseling protocol demonstrated effective coping skills and absence of negative psychological reactions after several months and found the testing to be beneficial, although the long-term effects of predictive testing for early onset Alzheimer disease (EOAD) remain to be seen.

Qualifying Statements

Qualifying Statements

- The practice guidelines of the National Society of Genetic Counselors (NSGC) and the American College of Medical Genetics (ACMG) are developed by members of the NSGC and ACMG to assist geneticists, genetic counselors, and other health care providers in making decisions about appropriate management of genetic concerns, including access to and/or delivery of services. Each practice guideline focuses on a clinical or practice-based issue, and is the result of a review and analysis of current professional literature believed to be reliable. As such, information and recommendations within the practice guidelines reflect the current scientific and clinical knowledge at the time of publication, are only current as of their publication date, and are subject to change without notice as advances emerge.
- In addition, variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guideline. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does the use of

such recommendations guarantee a particular outcome. Genetic counseling practice guidelines are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient or patient population. Practice guidelines are published by NSGC and ACMG for educational and informational purposes only, and NSGC and ACMG do not "approve" or "endorse" any specific methods, practices, or sources of information. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, Strecker MN, Roberts JS, Burke W, Mayeux R, Bird T, American College of Medical Genetics and the National Society of Genetic Counselors. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011 Jun;13(6):597-605. [118 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jun

Guideline Developer(s)

American College of Medical Genetics and Genomics - Professional Association

National Society of Genetic Counselors - Medical Specialty Society

Source(s) of Funding

National Society of Genetic Counselors

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

Authors: Jill S. Goldman, MS, MPhil, Department of Nephrology, Sergievsky Center and Taub Institute for Research on Alzheimer Disease and the Aging Brain, Columbia University, New York City, New York; Susan E. Hahn, MS, John P. Hussman Institute for Human Genomics, University of Miami, Miller School of Medicine, Miami, Florida; Jennifer Williamson Catania, MS, MPH, Department of Nephrology, Sergievsky Center and Taub Institute for Research on Alzheimer Disease and the Aging Brain, Columbia University, New York City, New York; Susan LaRusse-Eckert, MS, Sergievsky Center and Taub Institute for Research on Alzheimer Disease and the Aging Brain, Columbia University, New York City, New York; Melissa Barber Butson, ScM, Department of Bioethics, Case Western Reserve University, Cleveland, Ohio; Malia Rumbaugh, MS, Department of Neurology, University of Washington, Seattle Institute of Biomedical and Clinical Research, Seattle, Washington; Michelle N. Strecker, MS, CombiMATRIX Diagnostics, Irvine, California, Division of Medical Genetics, University of California San Francisco, San Francisco, California; J. Scott Roberts, PhD, Department of Health Behavior & Health Education, University of Michigan School of Public Health, Ann Arbor, Michigan; Wylie Burke, MD, PhD, Department of Bioethics and Humanities; Richard Mayeux, MD, MSc, Department of Nephrology, Sergievsky Center and Taub Institute for Research on Alzheimer Disease and the Aging Brain, Columbia University, New York City, New York; and Thomas Bird, MD, Division of Neurogenetics, University of Washington, Seattle, Washington

Financial Disclosures/Conflicts of Interest

The authors declare no conflict of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Genetics in Medicine Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 26, 2013. The information was verified by the guideline developer on March 25, 2013.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.